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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,031	GUELLY ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,23,27-33,47-66,69,71-79 and 82-85* is/are pending in the application.

4a) Of the above claim(s) *22,23,27-33,47-65 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66, 69, 71-79, and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 1/28/08 in response to the Office Action of 7/27/07 are acknowledged and have been entered.

Claims 22, 23, 27-33, 47-66, 69, 71-79, and 82-85 are pending.

Claims 22, 23, 27-33, 47-65, and 82-84 have been withdrawn.

Claims 66, 69, 74, 76, and 79 have been amended by Applicant.

Claims 66, 69, 71-79, and 85 are currently under examination.

Rejections Withdrawn

The rejection of claim 66 under 35 U.S.C. 112, second paragraph, is withdrawn.

The rejection of claim 66 under 35 U.S.C. 102(b) is withdrawn. However, as discussed below, claims 69 and 71-79 remain rejected under 35 U.S.C. 102(b).

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66 and 85 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons stated in the Office Action of 7/27/07 and for the reasons set-forth below. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action of 7/27/07 contains the following text:

"The Office Action of 1/9/07 indicated that while being enabling for a method for diagnosing hepatocellular carcinoma in a patient comprising comparing the expression level of a polynucleotide comprising the sequence set forth in SEQ ID NO:11 in a first blood sample from said patient with the expression level of said polynucleotide in a second corresponding blood sample from a subject known to be free of hepatocellular carcinoma wherein elevated expression of SEQ ID NO:11 in the first blood sample as compared to the second blood sample indicates hepatocellular carcinoma, the specification does not reasonably provide enablement for a method of diagnosing hepatocellular carcinoma using just any type of patient sample is compared to just any type of sample or just of any type of reference library or of any other sample.

In the Reply of 5/31/07, Applicant indicates that claim 66 has been amended to recite "a blood sample". However, no such amendment is found in claim 66 or 85.

The amendments to the claims and the arguments found in the Reply of 5/31/07 have been carefully considered, but are not deemed persuasive. For the reasons stated in the Office Action of 1/9/07, specifically that one of skill would not predict SEQ ID NO:11 expression in just any patient and control sample to function in the claimed method with an expectation of success, the rejection is maintained."

In the Reply of 1/28/08, Applicant argues that the "patient/reference samples" in claim 66 have been amended to "liver tissue, a liver cell, blood, serum, plasma". Applicant further points-out that the specification provides results that RNA of SEQ ID NO:11 is upregulated in HCC livers as compared to RNA of reference livers (lines 27-28 of page 23, in particular) and the teaching of Panzitt et al (Gastroenterology, 2007, 132(1): 330-342) support this finding. Applicant further points-out that the specification discloses that RNA of SEQ ID NO:11 is not detected in tumor stroma of patients with HCC (lines 6-9 of page 24, in particular).

The amendments to the claims and the arguments found in the Reply of 1/28/08 have been carefully considered, but are not deemed persuasive. In regards to the argument that the “patient/reference samples” in claim 66 have been amended to "liver tissue, a liver cell, blood, serum, plasma", the “patient/reference samples” in claim 66 have *not* been amended to "liver tissue, a liver cell, blood, serum, plasma". The claims encompass methods wherein the reference samples can be any non-diseased control. Further, Applicant amended the samples from the patient as those "selected from the group consisting of liver tissue, a liver cell, **tissue**, blood, serum, and plasma”. The term “tissue” encompasses any tissue. As evidenced by the specification, RNA of SEQ ID NO:11 is not detected in tumor stroma of patients with HCC (lines 6-9 of page 24, in particular). The term "tissue" encompasses tumor stroma. Therefore, the specification provides evidence that the method would not predictably function using just any tissue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 69 and 71-79 remain rejected under 35 U.S.C. 102(b) as being anticipated by Horne et al (WO 02/29103 A2; 4/11/02) for the reasons stated in the Office Action of 7/27/07 and for the reasons stated below.

The Office Action of 7/27/07 contains the following text:

"Horne et al teaches a polynucleotide sequence, Sequence #2645, which consists of a 176 base pair polynucleotide sequence that shares 95.6% homology with 176 consecutive base pairs of instant SEQ ID NO:11 (see attached sequence comparison). Because of the high degree of homology of Sequence #2645 to a region of instant SEQ ID NO:11, one of skill in the art would recognize that reagents used to identify Sequence #2645, including polynucleotide complements of Sequence #2645, would detect polynucleotides comprising instant SEQ ID NO:11. Horne et al further teaches a method of diagnosis of hepatocellular carcinoma wherein expression of a polynucleotide comprising SEQ ID NO:11 would be identified in a blood sample from patient and compared with expression of a polynucleotide comprising SEQ ID NO:11 in a reference library or a reference blood sample from a non-diseased control, wherein overexpression of polynucleotides comprising SEQ ID NO:11 is indicative of a diagnosis of hepatocyte carcinoma (page 11 lines 20-33, in particular). Further, Horne et al teaches a method of diagnosing hepatocellular carcinoma comprising the following steps: (a) detecting the expression of a polynucleotide comprising SEQ ID NO:11 in a blood sample isolated from a patient, (b) comparing said expression with the expression of polynucleotides comprising SEQ ID NO:11 in a reference library or in a reference blood sample, (c) identifying polynucleotides which are differentially expressed between the blood sample isolated from the patient as compared to the reference library or the reference blood sample, and (d) matching said nucleic acid(s) identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference blood or sample or pathologic reference library, wherein the matched nucleic acid(s) is (are) indicative of the patient suffering from a hepatocellular carcinoma (page 11 lines 20-33, in particular). Horne et al further teaches a method wherein said nucleic acids are detected by PCR based detection or by a hybridization assay (page 13, in particular). Horne et al further teaches a method wherein the expression of said nucleic acids are compared by a solid-phase based screening methods (page 19, in particular). Horne et al further teaches a method wherein the patient sample is blood (page 18 lines 25-30, in particular). Horne et al further teaches a method wherein the reference sample is isolated from a source selected from a non-diseased blood sample from another subject (page 11 lines 20-33 and page 18 lines 25-30, in particular). Horne et al further teaches a method wherein the reference library is an expression library or a data base comprising clones or data on hepatocellular carcinoma-specific expression of SEQ ID NO:11 (pages 11, 21, and 22, in particular)."

In the Reply of 5/31/07, Applicant indicates that the Horne sequence (SEQ ID NO:2645) is taught to be down-regulated in metastatic malignant liver (secondary liver cancer), which Applicant states is the opposite expression pattern compared to elected SEQ ID NO:11 (which Applicant states is up-regulated in HCC). Applicant states that it is clear that the sequence in Horne is related to a different form of cancer from that of the claimed invention and Horne et al teaches a different type of expression (down-regulation) as compared to the instantly claimed type of expression (over-expression). Applicant states that there is no suggestion in Horne to use SEQ ID NO:2645 as a hepatocellular carcinoma biomarker. Applicant further argues that Horne does not teach a polynucleotide consisting of or comprising of instant SEQ ID NO:11.

The amendments to the claims and the Arguments found in the Reply of 5/31/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the Horne sequence (SEQ ID NO:2645) is taught to be down-regulated in metastatic malignant liver (secondary liver cancer), which Applicant states is the opposite expression pattern compared to elected SEQ ID NO:11 (which Applicant states is up-regulated in HCC), Applicant is arguing limitations not recited in the claims. The pending claims do not require SEQ ID NO:11 to be upregulated in hepatocellular carcinoma samples as compared to a control. Rather, pending claim 66 requires that overexpression of SEQ ID NO:11 as compared to a non-diseased control is "indicative of" a diagnosis of hepatocellular carcinoma. Claim 66 does not clearly point out whether over-expression of the identified polynucleotide(s) in a biological sample as compared to the non-diseased control indicates that the patient from which the biological sample was derived *has* hepatocellular carcinoma *or* whether over-expression of the identified polynucleotide(s) in a biological sample as compared said non-diseased control indicates that the patient from which the biological sample was derived *does not have* hepatocellular carcinoma (see 35 U.S.C. 112, second paragraph, rejection above). Therefore, the pending claims broadly read on the teaching of Horne (see lines 7-10 of page 3, in particular), which teaches differential expression of SEQ ID NO:2645 is indicative of liver cancer (wherein upregulation would be "indicative of" liver cancer). It is further noted that possible limitations disclosed in the specification are not read into the claims. In regards to the argument that Horne does not teach a polynucleotide consisting of or comprising of instant SEQ ID NO:11, as indicated in the Office Action of 1/9/07, due to the high degree of homology (95.6%) between the sequence taught by Horne et al and a region of instant SEQ ID NO:11, one of skill in the art would recognize that complements of the sequence taught by Horne et al *would* identify instant SEQ ID NO:11."

In the Reply of 1/28/08, Applicant argues that Horne et al does not teach methods requiring using a "polynucleotide consisting of the polynucleotide sequence of SEQ ID NO:11 or a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:11" and diagnosis by detecting up-regulation. Applicant further argues that Horne et al does not teach SEQ ID NO:11, but rather teaches a sequence that shares 95.6% homology to Exon 2 region of clone 5 = SEQ ID NO:11. Applicant further agues that Horne et al teaches a sequence that is down-regulated in metastatic malignant liver (secondary liver cancer), thus exhibiting the opposite disclosed expression pattern of

SEQ ID NO:11 (which is disclosed to be upregulated in primary liver cancer). Applicant further argues that the sequence taught by Horne is not an optimal hepatocellular carcinoma biomarker and there is no suggestion in Horne to use this sequence for such.

The amendments to the claims and the arguments found in the Reply of 1/28/08 have been carefully considered, but are not deemed persuasive in regards to claims 69 and 71-79. In regards to the arguments that Horne et al does not teach methods requiring using a "polynucleotide consisting of the polynucleotide sequence of SEQ ID NO:11 or a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:11" and diagnosis by detecting up-regulation, instant claims 69 and 71-79 do not recite "use" of polynucleotides consisting or comprising SEQ ID NO:11 or methods of diagnosis by detecting up-regulation. Rather, instant claims 69 and 71-79 recite methods comprising "detecting" polynucleotides comprising SEQ ID NO:11 and do not recite which reagents are to be "used" to detect said polynucleotides. Further, as stated in the Office Action of 7/27/07 and as indicated in the Office Action of 1/9/07, due to the high degree of homology (95.6%) between the sequence taught by Horne et al and a region of instant SEQ ID NO:11, one of skill in the art would recognize that complements of the sequence taught by Horne et al *would* identify instant SEQ ID NO:11. In regards to the argument that the sequence taught by Horne is not an optimal "hepatocellular carcinoma biomarker" and there is no suggestion in Horne to use this sequence for such, Horne et al teaches every active method step recited in claims 69 and 71-79. It is further noted that detection of SEQ ID NO:11 to identify "a polynucleotide differentially expressed in a sample isolated from a patient to be

diagnosed for “hepatocellular carcinoma” relative to a reference library or a reference sample from a non-diseased control” is recited in the preamble of claim 69 and is not considered a limitation of claim 69. Further, use of "an optimal" hepatocellular carcinoma biomarker is not recited in the instant claims.

Summary

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SEA

/MISOOK YU/

Primary Examiner, Art Unit 1642